ClinicalEvidence

Leprosy

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ABSTRACT

INTRODUCTION: The World Health Organization field leprosy classification is based on the number of skin lesions: paucibacillary leprosy (1–5 skin lesions), and multibacillary leprosy (more than 5 skin lesions). Worldwide, about 250,000 new cases of leprosy are reported each year, and about 2 million people have leprosy-related disabilities. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent leprosy? What are the effects of treatments for leprosy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 20 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: chemoprophylaxis with single-dose rifampicin, Bacillus Calmette–Guerin (BCG) plus killed Mycobacterium leprae vaccine, BCG vaccine, ICRC vaccine, multidrug treatment, multiple-dose treatment, Mycobacterium w vaccine, and single-dose treatment.

QUESTIONS

INTERVENTIONS

PREVENTION OF LEPROSY

Beneficial

Likely to be beneficial

TREATMENTS FOR LEPROSY

Likely to be beneficial

To be covered in future updates

Treatment of reactions

Footnote

*Categorisation based on observational evidence and consensus; RCTs unlikely to be conducted.

Key points

- Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*, primarily affecting the peripheral nerves and skin.

  The WHO field leprosy classification is based on the number of skin lesions: paucibacillary leprosy (1–5 skin lesions), and multibacillary leprosy (more than 5 skin lesions).

  Worldwide, about 250,000 new cases of leprosy are reported each year, and about 2 million people have leprosy-related disabilities.

- Chemoprophylaxis given to contacts of index cases is moderately effective in preventing leprosy.

  Chemoprophylaxis with single-dose rifampicin reduces the incidence of leprosy in contacts of new cases, although the effect is only seen in the first 2 years.

- Vaccination is the most efficient method of preventing the contraction of leprosy.

  Vaccination with Bacillus Calmette–Guerin (BCG) vaccine, either alone or in combination with killed *M leprae* , reduces the incidence of leprosy. BCG and BCG plus killed *M leprae* seem to be as effective as each other at reducing the incidence of leprosy.

  ICRC vaccine prevents leprosy and produces few adverse effects, although its formulation is unclear and we only found evidence in one geographical area.

  Mycobacterium w vaccine reduces the incidence of leprosy compared with placebo.

- Leprosy is generally treated with multidrug programmes.

  Despite sparse good RCT or cohort study evidence, there is consensus that multidrug treatment (rifampicin plus clofazimine plus dapsone) is highly effective for treating multibacillary leprosy. Placebo-controlled trials of multidrug treatment would now be considered unethical.

  Multidrug treatment with rifampicin plus dapsone is believed to improve skin lesions, nerve impairment, and relapse rates in people with paucibacillary leprosy, despite a lack of good evidence.

  Multiple-dose treatments with rifampicin monthly plus dapsone daily for 6 months are more effective than single-dose treatments with rifampicin plus minocycline plus ofloxacin for treating people with single skin lesions (although both achieve high cure rates).

DEFINITION

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*, primarily affecting the peripheral nerves and skin. The clinical picture depends on the individual's immune response to *M leprae*. At the tuberculoid end of the Ridley–Jopling scale, individuals have good cell-mediated immunity and few skin lesions. At the lepromatous end of the scale, individuals have low reactivity for *M leprae*, causing uncontrolled bacterial spread and skin and mucosal infiltration. Peripheral nerve damage occurs across the spectrum. Nerve damage may occur before, during, or after treatment. Some people have no nerve damage, while others develop anaesthesia of the hands and feet, which puts them at risk of developing neuropathic injury. Weakness and paralysis of the small muscles of the hands, feet, and eyes put people at risk of developing deformity and contractures. Loss of the fingers and toes is caused by repeated injury in a weak, anaesthetic limb. These visible deformities cause stigmatisation. Classification is based on clinical appearance and bacterial index of lesions. The WHO field leprosy classification is based on the number of skin lesions: paucibacillary leprosy (1–5 skin lesions) and multibacillary leprosy (more than 5 skin lesions). [1]

INCIDENCE/ PREVALENCE

Worldwide, about 250,000 new cases of leprosy are reported each year, [2] and about 2 million people have leprosy-related disabilities. [3] Three major endemic countries (India, Brazil, and Indonesia) account for 77% of all new cases. [2] Cohort studies show a peak of disease presentation between 10 and 20 years of age. [4] After puberty, there are twice as many cases in males as in females.

AETIOLOGY/ RISK FACTORS

M leprae is discharged from the nasal mucosa of people with untreated lepromatous leprosy, and spreads, via the recipient's nasal mucosa, to infect their skin and nerves. It is a hardy organism and has been shown to survive outside human hosts in India for many months. [5] Risk factors for infection, when known, include household contact with a person with leprosy. We found no good evidence of an association with HIV infection, nutrition, or socioeconomic status. [6] [7] [8]

PROGNOSIS

Complications of leprosy include nerve damage, immunological reactions, and bacillary infiltration. Without treatment, tuberculoid infection eventually resolves spontaneously. Most people with borderline tuberculoid and borderline lepromatous leprosy gradually develop lepromatous infection. Many people have peripheral nerve damage at the time of diagnosis, ranging from 15% in Bangladesh [9] to 55% in Ethiopia. [10] Immunological reactions can occur with or without antibiotic treatment. Further nerve damage occurs through immune-mediated reactions (type 1 reactions) and neuritis. Erythema nodosum leprosum (type 2 reactions) is an immune complex-mediated reaction causing fever, malaise, and neuritis, which occurs in 20% of people with lepromatous leprosy, and in 5% with borderline lepromatous leprosy. [11] Secondary impairments (wounds, contractures, and digit resorption) occur in 33% to 56% of people with established nerve damage. [12] We found no recent information on mortality.

AIMS OF INTERVENTION

Prevention: To prevent infection. **Treatment:** To treat infection and improve skin lesions; to prevent relapse and complications (nerve damage and erythema nodosum leprosum). Prevention of complications such as ulcers and deformity may improve the quality of life for the individual and help to reduce the severe stigmatisation that still accompanies leprosy.

OUTCOMES

Prevention: Incidence of leprosy. **Treatment:** Clinical improvement, relapse rate, quality of life, mortality, and adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal September 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2009, Embase 1980 to September 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to

the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, including open studies, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We also did an observational search for controlled clinical trials for all questions, prospective and retrospective cohort studies with or without control groups and case series with more than 50 patients for drug treatment questions. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions to prevent leprosy?

OPTION CHEMOPROPHYLAXIS WITH SINGLE-DOSE RIFAMPICIN New

Incidence of leprosy
Compared with placebo Single-dose rifampicin is more effective at reducing the incidence of leprosy at 1 to 2 years in contacts of people with leprosy. However, single-dose rifampicin seems no more effective at reducing incidence of leprosy at 3 to 4 years in contacts of people with leprosy (moderate-quality evidence).

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits: **Chemoprophylaxis with single-dose rifampicin versus placebo or no treatment:**
We found one RCT (21,711 close contacts of 1037 people newly diagnosed with leprosy in Bangladesh) comparing chemoprophylaxis with single-dose rifampicin (300–600 mg depending on age and weight) versus placebo. [13] It found that, compared with placebo, single-dose rifampicin significantly reduced the proportion of contacts diagnosed with leprosy in the 1- to 2-year period following enrolment (29/9951 [0.3%] with rifampicin *v* 67/10,006 [0.7%] with placebo; 57% reduction of leprosy with rifampicin, 95% CI 33% to 72%; P = 0.0002). It found no significant difference in the proportion of contacts diagnosed with leprosy in the 3- to 4-year period following enrolment between single-dose rifampicin and placebo (30/9388 [0.3%] with rifampicin *v* 24/9361 [0.3%] with placebo; P greater than 0.05); however, over the whole 1- to 4-year follow-up period, rifampicin significantly reduced the proportion of contacts diagnosed with leprosy (absolute numbers not reported; 35% reduction of leprosy with rifampicin, 95% CI 10% to 53%; P = 0.02).

Harms: **Chemoprophylaxis with single-dose rifampicin versus placebo or no treatment:**
The RCT gave no information on adverse effects. [13]

Comment: Other studies have used other chemoprophylactic regimens, such as double-dose rifampicin, [14] or a single dose of rifampicin plus ofloxacin plus minocycline (ROM); [15] results are broadly in line with those described for single-dose rifampicin, which has the advantages of being cheaper to administer and has fewer potential adverse effects.

OPTION BACILLUS CALMETTE GUERIN VACCINE

Incidence of leprosy
Compared with placebo or no treatment BCG vaccine may be more effective at reducing the incidence of leprosy (low-quality evidence).

Compared with BCG plus M leprae vaccine BCG vaccine alone is equally effective at reducing the incidence of leprosy (high-quality evidence).

BCG revaccination compared with no BCG revaccination We don't know whether BCG revaccination is more effective at reducing the incidence of leprosy (very low-quality evidence).

Adverse effects
BCG vaccine alone is associated with minimal adverse effects.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits:

Bacillus Calmette–Guerin (BCG) versus placebo or no treatment:
We found two systematic reviews (search dates 2005 [16] and 2006 [17]). The first systematic review included 26 experimental and observational studies (1 RCT, 6 non-randomised controlled trials, and 19 cohort and case control studies). [16] The second systematic review included 29 experimental studies in 32 references (1 RCT, 12 non-randomised controlled trials, and 16 cohort and case control studies). The two systematic reviews had 22 studies in common.

The first systematic review performed a meta-analysis of the experimental studies and found an overall protective effect associated with BCG vaccine after 5 to 16 years' follow-up (7 studies; RRR 26%, 95% CI 14% to 37%). Meta-analysis of the observational studies also found an overall protective effect associated with BCG vaccine at 4 to 5 years' follow-up (19 studies; RRR 61%, 95% CI 51% to 70%). The authors of the review noted that the meta-analysis of observational studies overestimated the protective effect of BCG. The reason for the higher protective efficacy in the observational studies might be that the observational studies had a shorter period of follow-up compared with the experimental studies, and protective efficacy seems to decrease with time. The systematic review found heterogeneity between studies in both meta-analyses. [16]

The second systematic review performed meta-analyses of experimental studies, cohort studies, and case control studies; all meta-analyses found that BCG vaccine significantly reduced the proportion of people with leprosy compared with no BCG vaccine (6 experimental studies, 373,183 people: 4690/231,093 [2%] with BCG vaccine *v* 3872/142,090 [3%] with no BCG vaccine; RR 0.57, 95% CI 0.45 to 0.73; 2 cohort studies, 162,066 people: 105/77,805 [0.1%] with BCG vaccine *v* 380/84,261 [0.5%] with no BCG vaccine; RR 0.38, 95% CI 0.31 to 0.73; 14 case control studies, 89,936 people: 1120/51,672 [2%] with BCG vaccine *v* 1367/38,264 [4%] with no BCG vaccine; OR 0.42, 95% CI 0.33 to 0.53; time frames not reported). [17] There was significant heterogeneity among trials for the meta-analyses of the experimental studies and the case control studies; however, the role of individual factors in explaining the heterogeneity could not be quantified. Although there was statistical heterogeneity, the authors pointed out that no study reported a negative protective effect, and concluded that there is sufficient and convincing evidence of the protective effect of BCG against leprosy.

A controlled clinical trial performed in Myanmar compared two different concentrations of BCG vaccine versus no treatment. [18] The vaccine with the higher concentration of bacilli significantly reduced the incidence of leprosy over 14 years (3.8/1000 person-years with BCG *v* 5.4/1000 person-years with control; RRR 30%, 95% CI 19% to 40%). The vaccine with the lower concentration of bacilli had no significant protective effect (5.0/1000 person-years with BCG *v* 5.6/1000 person-years with control; RRR +11%, 95% CI –3% to +23%).

BCG alone versus BCG plus killed *Mycobacterium leprae*:
See benefits of BCG plus killed *Mycobacterium leprae*, p 5 .

BCG revaccination (with BCG or BCG plus killed *M leprae*) versus no BCG revaccination:
We found two RCTs comparing BCG revaccination versus no BCG revaccination. [19] [20]

The first RCT (121,020 people aged 0.25–75 years carried out in Malawi) stratified people according to the presence of a BCG scar. [19] Those with a scar or a possible scar (54,865 people) received either BCG, BCG plus killed *M leprae*, or placebo. The RCT found that combined results for revaccination with BCG or BCG plus killed *M leprae* significantly reduced the incidence of diagnostically certain cases of leprosy post-vaccination compared with placebo at 5 to 9 years (12/23,456 [0.05%] with BCG *v* 23/23,307 [0.1%] with placebo; RR 0.51, 95% CI 0.26 to 0.99).

The second RCT (carried out in Brazil, 92,770 school children aged 7 to 14 years who had received neonatal BCG and who had 1 BCG scar) compared revaccination with BCG vaccine versus no revaccination (children were not given a placebo). [20] The children were followed up for 6 years and 8 months. The RCT found no significant difference in the incidence of leprosy between the revaccination and no revaccination groups (56/42,662 [1.71 per 10,000 person-years] with BCG revaccination *v* 59/50,108 [1.59 per 10,000 person-years] with no BCG revaccination; rate ratio 0.99, 95% CI 0.69 to 1.43). The analysis presented here is a subgroup of children with one BCG scar; 153,438 were originally enrolled in the study. The study had quality issues, such as cluster randomisation and lack of adherence to completing the standard questionnaire for diagnosing leprosy.

Harms:

Bacillus Calmette–Guerin (BCG) versus placebo or no treatment:
The systematic reviews [16] [17] and other trials [21] [19] [18] identified by the review gave no information on adverse effects. The controlled clinical trial gave no information on adverse effects. [18]

BCG alone versus BCG plus killed *Mycobacterium leprae*:
See harms of BCG plus killed *Mycobacterium leprae*, p 5 .

BCG revaccination (with BCG or BCG plus killed *M leprae*) versus no BCG revaccination:
The first RCT gave no information on adverse effects. [19] The second RCT assessed adverse effects in only the revaccination group. [20] Adverse effects related to the BCG vaccine were reported in 18/47,307 (3.80 events per 10,000 children). Eight adverse events were ulcer greater than 1 cm; seven adverse events were cold abscess; and three adverse events were axillary lymph node enlargement without suppuration, "hot" abscess with suppuration, and nodule in vaccination site. The RCT found no significant difference in adverse effects between children without a previous BCG scar and children with one previous BCG scar (3/8176 [3.67 events per 10,000 children] without a previous BCG scar *v* 15/39,067 [3.84 events per 10,000 children] with one BCG scar; risk ratio adjusted for clustering, sex, and year of birth 1.05, 95% CI 0.31 to 3.53).

Comment:

One of the trials included in both systematic reviews also looked at mortality, and found that BCG vaccination was associated with a significant reduction in mortality compared with saline (deaths from all causes: 442/2707 [16%] with BCG *v* 489/2649 [19%] with saline; RR 0.89, 95% CI 0.79 to 0.99; NNT 47, 95% CI 24 to 997). [21]

In the trial in Malawi, 7/92 (8%) people with post-vaccination leprosy who were tested for HIV were positive for HIV. [19] Eleven different batches of BCG were used. The proportion of people examined at least once after vaccination was 64%, and the sample size may have been insufficient to rule out clinically important effects, given that there were multiple comparisons against placebo.

OPTION BACILLUS CALMETTE–GUERIN PLUS KILLED MYCOBACTERIUM LEPRAE VACCINE

Incidence of leprosy
Compared with placebo BCG plus killed M leprae vaccine is more effective at reducing the incidence of leprosy compared with placebo (moderate-quality evidence).

Compared with BCG vaccine alone BCG plus killed M leprae vaccine is equally effective at reducing the incidence of leprosy (high-quality evidence).

Adverse effects
BCG plus killed M leprae vaccine is associated with minimal adverse effects.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits:

BCG plus killed *Mycobacterium leprae* versus placebo:
We found one five-arm RCT (double blind, 171,400 healthy people in India aged 1–65 years), carried out in a leprosy-endemic area in India, with clinical leprosy as the outcome measure. [22] The RCT compared four vaccines (BCG: 38,213 people with 6–7 years of follow-up; BCG plus killed *M leprae*: 38,229 people with 2–4 years of follow-up; ICRC vaccine: 22,541 people with 2–4 years of follow-up; and *Mycobacterium w* vaccine: 33,720 people with 2–4 years of follow-up) versus normal saline (38,697 people with 6–7 years' follow-up); data for the individual vaccines are reported in the appropriate interventions. The RCT included a statistical adjustment for the multiple comparisons against saline. The RCT found that BCG plus killed *Mycobacterium leprae* significantly reduced the incidence of leprosy compared with saline (BCG plus killed *M leprae v* saline, RRR 64.0%, 95% CI 50.4% to 73.9%; absolute numbers not reported).

BCG plus killed *Mycobacterium leprae* versus BCG alone:
We found one RCT (121,020 people aged 0.25–75 years) carried out in Malawi. [19] The RCT stratified people according to the presence of a BCG scar. Those without a scar (66,155 people) received BCG plus killed *M leprae* or BCG. The RCT found no significant difference in the incidence of diagnostically certain cases of leprosy post-vaccination between BCG plus killed *M leprae* or BCG at 5 to 9 years (33/38,251 [0.09%] with BCG plus killed *M leprae v* 23/27,904 [0.08%] with BCG; RR 1.06, 95% CI 0.62 to 1.82).

Harms:

BCG plus killed *Mycobacterium leprae* versus placebo:
The RCT conducted in India found that "fluctuant adenitis" was minimal with all four vaccines used, and no other adverse effects were observed (numbers not reported). [22]

BCG plus killed *Mycobacterium leprae* versus BCG alone:
The RCT gave no information on adverse effects. [19]

Comment: None.

OPTION ICRC VACCINE

Incidence of leprosy
Compared with placebo ICRC vaccine seems more effective at reducing the incidence of leprosy (moderate-quality evidence).

Adverse effects
The ICRC vaccine is associated with minimal adverse effects. The formulation of ICRC vaccine is unclear, and we only found evidence in one geographical region.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits: **ICRC vaccine versus placebo:**
We found one five-arm RCT (double blind, 171,400 healthy people in India aged 1–65 years), carried out in a leprosy-endemic area in India, with clinical leprosy as the outcome measure. [22] The RCT compared four vaccines (BCG: 38,213 people with 6–7 years of follow-up; BCG plus killed *M leprae*: 38,229 people with 2–4 years of follow-up; ICRC vaccine: 22,541 people with 2–4 years of follow-up; and *Mycobacterium w* vaccine: 33,720 people with 2–4 years of follow-up) versus normal saline (38,697 people with 6–7 years' follow-up); data for the individual vaccines are reported in the appropriate interventions. The RCT included a statistical adjustment for the multiple comparisons against saline. The RCT found that ICRC vaccine significantly reduced the incidence of leprosy compared with saline (ICRC *v* saline, RRR 65.5%, 95% CI 48.0% to 77.0%; absolute numbers not reported).

Harms: **ICRC vaccine versus placebo:**
The RCT conducted in India found that "fluctuant adenitis" was minimal with all four vaccines used, and no other adverse effects were observed (numbers not reported). [22]

Comment: **Clinical guide:**
We only found evidence of ICRC vaccine in one region with leprosy (India). The formulation of the vaccine is unclear.

OPTION MYCOBACTERIUM W VACCINE

Incidence of leprosy
Compared with placebo Mycobacterium w vaccine seems more effective at reducing the incidence of leprosy (moderate-quality evidence).

Adverse effects
Mycobacterium w vaccine is associated with minimal adverse effects.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits: ***Mycobacterium w* vaccine versus placebo:**
We found two RCTs. [23] [22] One cluster RCT (randomisation by village, 272 villages stratified by size and leprosy prevalence; 29,420 household contacts assessed) compared four different vaccination strategies for people with leprosy and their household contacts: patient and contacts both vaccinated, only patient vaccinated, only contacts vaccinated, and placebo for both patient and contacts. [23] It found that *Mycobacterium w* vaccination of patients and contacts or contacts alone had a protective effect compared with placebo at up to 9 years. In an analysis of only contacts (vaccinated), the RCT found that *Mycobacterium w* vaccine significantly reduced the proportion of contacts who had leprosy at 9 to 10 years compared with placebo (87/5410 [2%] with vaccine *v* 136/5188 [3%] with placebo; P = 0.0003; OR 0.607, 95% CI 0.458 to 0.804). The RCT also found that *Mycobacterium w* vaccine reduced the proportion of contacts who had leprosy at 9 to 10 years compared with placebo when people with leprosy had also received vaccine, but statistical analysis for this comparison was not reported (93/4889 [2%] with vaccine *v* 126/4969 [3%] with placebo; P value not reported).

We also found one five-arm RCT (double blind, 171,400 healthy people in India aged 1–65 years), carried out in a leprosy-endemic area in India, with clinical leprosy as the outcome measure. [22] The RCT compared four vaccines (BCG: 38,213 people with 6–7 years of follow-up; BCG plus killed *M leprae*: 38,229 people with 2–4 years of follow-up; ICRC vaccine: 22,541 people with 2–4

years of follow-up; and *Mycobacterium w* vaccine: 33,720 people with 2–4 years of follow-up) versus normal saline (38,697 people with 6–7 years' follow-up); data for the individual vaccines are reported in the appropriate interventions. The RCT included a statistical adjustment for the multiple comparisons against saline. The RCT found that *Mycobacterium w* vaccine significantly reduced the incidence of leprosy compared with saline (*Mycobacterium w v* saline, RRR 25.7%, 95% CI 1.9% to 43.8%; absolute numbers not reported).

Harms:

***Mycobacterium w* vaccine versus placebo:**
The cluster RCT comparing *Mycobacterium w* vaccination versus placebo found no major adverse effects, although there were some cases of injection-site induration and ulceration. [23]

The RCT conducted in India found that "fluctuant adenitis" was minimal with all four vaccines used, and no other adverse effects were observed (numbers not reported). [22]

Comment: None.

QUESTION What are the effects of treatments for leprosy?

OPTION MULTIDRUG TREATMENT FOR MULTIBACILLARY LEPROSY

Clinical improvement
Multidrug treatment One small case series found that, in people with multibacillary leprosy, 29% of lesions were still active at 3 years after multidrug treatment, and that the proportion of people with visible deformity increased from 8% at enrolment to 13% at 8 to 10 years of follow-up. Another case series found that 96% of people enrolled had neurological pathology after treatment (very low-quality evidence).

Relapse rates
Multidrug treatment Case series have reported relapse rates after multidrug treatment of 0/1000 person-years in Ethiopia to 20.4/1000 person-years in India (low-quality evidence).

Adverse effects
The incidence of adverse effects with multidrug treatment is unclear.

Note
There is consensus that multidrug treatment for multibacillary leprosy is likely to be beneficial.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits:

We found seven case series assessing the effects of multidrug treatment (MDT) taken for 24 months. [24] [25] [26] [27] [28] [29] [30]

Skin lesions:
One study in Thailand (53 people) found that 29% of lesions were still active at 3 years (see table 1, p 13). [24]

Nerve impairment:
The study in Thailand found that the proportion of people with visible deformity (WHO grade II) increased from 8% at enrolment to 13% at 8 to 10 years of follow-up (see table 1, p 13). [24]

Relapse:
Seven case series reported relapse rates (generally defined as a person successfully completing MDT, but subsequently developing signs or symptoms of leprosy either during a surveillance period or afterwards [31]). [24] [25] [26] [27] [28] [29] [30] Relapse rates varied from 0/1000 person-years in Ethiopia [25] to 20.4/1000 person-years in India [28] (see table 1, p 13). A retrospective study in Portugal found an overall relapse rate of 8.8%, but almost half the patients had received dapsone monotherapy before MDT, making it not strictly comparable with the other studies. [30]

Harms:

Most case series did not report on adverse effects. [26] [27] [28] One case series reported adverse effects in 2/46 (4%) people. [29] The adverse effects were dapsone syndrome and cutaneous reaction. [29] In one study, hepatitis due to rifampicin occurred in 1/188 (0.5%) people with multibacillary or paucibacillary leprosy, but the method of diagnosis was not reported. [24] The retrospective case series in Portugal found that 3/112 (3%) people developed influenza-like symptoms and 2/112 (2%) developed renal failure while receiving MDT. Reversal reactions occurred in 21/112 (19%) people and erythema nodosum leprosum occurred in 20/112 (18%) people. Leprosy reactions occurred before MDT in 29/41 (71%) people. [30]

See also harms of Multidrug treatment for paucibacillary leprosy, p 8

Comment:

We found one RCT (93 people with untreated lepromatous leprosy), which compared dapsone 50 mg daily plus rifampicin 450 mg daily versus dapsone 50 mg daily plus rifampicin 1200 mg monthly for the first 6 months of treatment. [28] It found no significant difference in clinical improvement between daily and monthly rifampicin (40/47 [85%] with daily rifampicin *v* 43/46 [91%] with monthly rifampicin; RR 0.91, 95% CI 0.62 to 1.03). Adverse effects were more common with daily than with monthly rifampicin, causing discontinuation in 8.5% of people with daily rifampicin compared with 0% with monthly rifampicin. [32]

We also found one RCT (189 people with leprosy [majority with borderline lepromatous or lepromatous leprosy] conducted in the Philippines), which compared four regimens: 1 year of MDT; 1 year of MDT plus 1 month of rifampicin and ofloxacin, 1 month of rifampicin and ofloxacin, and 2 years of MDT. [33] The RCT found significantly higher relapse rates with 1 month of rifampicin and ofloxacin than with the other three groups at 9 and 12 years, and found no significant difference in relapse rates among the remaining three groups.

Skin pigmentation may occur with clofazimine, which may be especially problematic in people with fair skin. [34]

Clinical guide:

Evidence from cases series of clinical improvement and relapse rates suggests that dapsone plus clofazimine plus rifampicin is effective for treating multibacillary leprosy, and studies comparing MDT versus placebo or no treatment would now be considered unethical. MDT was not compared with dapsone alone because rising dapsone resistance rates would make such a study unethical. Only one case series stratified results according to bacterial index. [28] The WHO study group on chemotherapy recommended that treatment be given for 24 months. [35] In 1998, the 7th Expert Committee gave the option of reducing the length of treatment from 24 months to 12 months. [1] We found one controlled trial that now supports this recommendation. [33] This RCT in the Philippines included 57 people in the group treated with 12 months' MDT and there was one relapse 6 years after treatment; this was considered an acceptable result.

OPTION MULTIDRUG TREATMENT FOR PAUCIBACILLARY LEPROSY

Clinical improvement

Multidrug treatment In people with paucibacillary leprosy, case series assessing multidrug treatment have reported resolution of lesions of 8% of people after 6 months, and 38% of people after 1 year. Reported rates of clinically active lesions after treatment range from 2% to 44%. Case series have reported increases in new disabilities at various lengths of follow-up after multidrug treatment (very low-quality evidence).

Relapse rates

Multidrug treatment The risk of relapse reported in case series in people with paucibacillary leprosy ranges from 0% over a mean of 4.1 years in Ethiopia and 0.33% over 5 years (0.66/1000 person-years) in China to 2.5% over 4 years (6.5/1000 person-years) in Malawi. It is clinically difficult to differentiate relapse from reaction in paucibacillary leprosy (very low-quality evidence).

Adverse effects

The incidence of adverse effects with multidrug treatment is unclear.

Note

There is consensus that multidrug treatment for paucibacillary leprosy is likely to be beneficial.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits:

We found seven case series, [24] [25] [26] [27] [36] [37] [38] and one 4-year follow-up from one of the case series, [39] assessing the effects of multidrug treatment (dapsone 100 mg/day plus rifampicin 600 mg monthly for 6 months), with follow-up ranging from 6 months to 10 years (see table 1, p 13). The studies used different methods of assessment, making it difficult to compare results. We also found one retrospective case series that assessed only adverse effects; [40] see harms section.

Skin lesions:

Three case series reported rates of resolution of skin lesions (one case series reported in 2 publications) (see table 1, p 13). [24] [36] [37] [39] One study (499 people) found that resolution of lesions occurred in 38% of people after 1 year; [37] another (50 people) found that resolution occurred in 8% of people after 6 months. [36] The proportion of people with lesions that were clinically active after treatment ranged from 2% to 44%. [24] [36] [37]

Nerve impairment:
Three case series reported rates of new or worsening nerve impairment (see table 1, p 13). [24] [39] [38] One study (499 people) found that new disabilities occurred in 2.5% of people, and that worsening of existing disabilities occurred in 3.3% after 4 years. [39] Another study (130 people) found that the visible disabilities (WHO grade II) increased from 4% at enrolment to 7% after 8 to 10 years of follow-up. [24] The third study found that, of the 21 people who relapsed, 5% had grade 1 deformity, 10% had grade 2 deformity, and 5% had grade 3 deformity (see table 1, p 13). [38]

Relapse:
Six case series reported relapse rates over a 3- to 8-year follow-up period (see table 1, p 13). [24] [25] [26] [27] [39] [38] The risk of relapse ranged from 0% over a mean of 4.1 years in Ethiopia [25] and 0.33% over 5 years (0.66/1000 person-years) in China [27] to 2.5% over 4 years (6.5/1000 person-years) in Malawi. [39] (It is clinically difficult to differentiate relapse from reaction in paucibacillary leprosy.)

Harms:

Most of the case series gave no information on adverse effects. [25] [26] [27] [39] [38] In one study, hepatitis due to rifampicin occurred in 1/188 (0.5%) people with multibacillary or paucibacillary leprosy, but the method of diagnosis was not reported. [24] One case series reported that 2/50 [4%] people had an increase in serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase levels. [36] In another study, 1/503 people (0.2%) suffered an "allergic reaction" to rifampicin and dapsone (details not reported). [37]

One retrospective case series from Brazil (194 people; 60% with paucibacillary leprosy; 40% with multibacillary leprosy; all treated with MDT) reported on adverse effects of MDT. [40] Adverse effects attributed to MDT (185 episodes) were reported in 88/194 (45%) people. Adverse effects were attributed to dapsone in 85/194 (44%) people, to rifampicin in 24/194 (13%) people, and to clofazimine in 18/194 (9%) people. Adverse effects attributed to dapsone included haemolytic anaemia (48/194 [25%]), gastrointestinal manifestations (23/194 [12%]), hepatic abnormalities (20/194 [10%]), dizziness (14/194 [7%]), headache (11/194 [6%]), psychiatric disorders (8/194 [4%]), skin reactions (6/194 [3%]), methahaemoglobinaemia (5/194 [3%]), muscle weakness (4/194 [2%]), and severe leukopenia (2/194 [1%]). Adverse effects attributed to rifampicin included hepatic abnormalities (10/194 [5%]), haemolytic anaemia (8/194 [4%]), gastrointestinal manifestations (5/194 [3%]), hypersensitivity (2/194 [1%]), and influenza-like syndrome (1/194 [0.5%]). Adverse effects attributed to clofazimine included gastrointestinal manifestations (17/194 [9%]) and lower-limb oedema (1/194 [0.5%]). A total of 46/194 (24%) people stopped treatment with dapsone, 5/194 (3%) people stopped treatment with rifampicin, and no one stopped treatment with clofazimine.

Comment:

Clinical guide:
In 1982, studies had shown that 30% of *Mycobacterium leprae* isolates were resistant to dapsone. [41] Therefore, the WHO introduced the combination of dapsone plus rifampicin urgently, without formal RCTs comparing it against dapsone, and such studies would now be considered unethical. Studies comparing multidrug treatment versus placebo or no treatment would also be considered unethical because of consensus regarding efficacy of multidrug treatment.

OPTION MULTIPLE-DOSE VERSUS SINGLE-DOSE TREATMENT FOR SINGLE SKIN LESIONS

Clinical improvement
Multiple-dose treatment compared with single-dose treatment Multiple-dose treatment with rifampicin monthly plus dapsone daily for 6 months may achieve higher clinical improvement rates at 18 months compared with single-dose treatment with rifampicin plus minocycline plus ofloxacin (low-quality evidence).

Adverse effects
Adverse effects are similar with both regimens.

For GRADE evaluation of interventions for leprosy, see table, p 15 .

Benefits:

Multiple-dose versus single-dose treatment:
We found one RCT (1483 people with single skin lesions typical of paucibacillary leprosy; see comment below) comparing single-dose treatment with rifampicin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg versus multiple-dose treatment with dapsone 100 mg daily plus rifampicin 600 mg monthly for 6 months. [42] Outcomes measured at 18 months were based on a scoring system involving five measurements: disappearance of the lesion, reduction in hypopigmentation, reduction in the degree of infiltration, reduction in the size of the lesion, and improvement in sensation in the lesion. Treatment failure was defined as no change or an increase in the clinical score; and marked improvement was defined as a difference of 13 between the baseline and 18-month scores. The RCT found that multiple-dose treatment significantly increased the proportion of people with marked improvement compared with single-dose treatment (392/684 [57%] with multiple dose *v*

361/697 [52%] with single dose; P = 0.04) and with complete cure (assessed clinically; 374/684 [55%] with multiple dose *v* 327/697 [47%] with single dose; RR 1.17, 95% CI 1.05 to 1.28; NNT 13, 95% CI 8 to 40). There were 12 treatment failures (6 in each group), and 99.1% of people in both groups had some improvement by the end of the study. [42]

Harms:

Multiple-dose versus single-dose treatment:
Allergic reactions (which were not specified) occurred in seven people (6 with multiple dose *v* 1 with single dose), and gastrointestinal effects occurred in five people (2 with multiple dose *v* 3 with single dose). There was no significant difference in the proportion of type 1 reactions (3/684 [0.4%] with multiple dose *v* 7/697 [1.0%] with single dose; ARI +0.6%, 95% CI –0.2% to +3.4%). [42]

Comment:

The RCT did not specify its diagnostic criteria and did not confirm the clinical diagnosis. The follow-up of only 18 months for people in the single-dose group is short for detection of relapse. Some infections in this group would have resolved spontaneously, and the absence of a placebo control group means that the treatment effect cannot be estimated. [42] Single-dose treatment has previously been assessed in people with paucibacillary leprosy. One RCT (622 people in Zaïre) compared two single-dose regimens: rifampicin 40 mg/kg plus clofazimine 1200 mg versus rifampicin 40 mg/kg plus clofazimine 100 mg plus dapsone 100 mg plus ethionamide 500 mg. It found that the overall relapse rate was 20.4/1000 person-years, which was substantially higher than the relapse rate found for 6 months of treatment with dapsone plus rifampicin, or rifampicin plus dapsone plus clofazimine.

Clinical guide:
Single-dose treatment has operational advantages in the field, particularly when people live in remote areas and are unable to attend a clinic for several months. [43]

GLOSSARY

Bacteriological index A measure of the density of *Mycobacterium leprae* in the skin. Slit skin smears are made at several sites, and the smears are stained and examined microscopically. The number of bacteria per high power field is scored on a logarithmic scale (0–6), and the index calculated by dividing the total score by the numbers of sites sampled.

ICRC vaccine A vaccine developed at the Indian Cancer Research Centre.

Multibacillary leprosy More than five skin lesions. [3]

Neuritis Inflammation of a nerve, presenting with any of the following: spontaneous nerve pain, paraesthesia, tenderness, or sensory, motor, or autonomic impairment.

Paucibacillary leprosy Between two and five skin lesions.

Type 1 (reversal) reaction A delayed type hypersensitivity reaction occurring at sites of *Mycobacterium leprae* antigen. It presents with acutely inflamed skin lesions and acute neuritis (nerve tenderness with loss of function).

Type 2 reaction or erythema nodosum leprosum An immunological complication of multibacillary leprosy presenting with short lived and recurrent crops of tender erythematous subcutaneous nodules that may ulcerate. There may be signs of systemic involvement with fever, and inflammation in lymph nodes, nerves, eyes, joints, testes, fingers, toes, or other organs.

World Health Organization disability grading A simple grading system for use in the field, mainly for collection of general data regarding disabilities. [1] Grade 0 = no anaesthesia, no visible deformity or damage; grade 1 = anaesthesia present, but no visible deformity or damage; grade 2 = visible deformity or damage present.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Person-years at risk The number of new cases of disease in a specified time period divided by the number of person-years at risk during that period (average number at risk of relapse multiplied by the length of observation).

Ridley–Jopling classification of people with leprosy This scale classifies people with leprosy according to their clinical features and bacterial load which reflect their immune response to *Mycobacterium leprae*. The scale forms a spectrum of people with tuberculoid leprosy (TT) and high cell-mediated immunity at one pole. These people have just one skin or nerve lesion. At the other pole is lepromatous leprosy (LL) with no cell-mediated immunity for *M leprae* and widespread disease with skin nodules and multiple nerve involvement. In between these poles are the borderline forms (Borderline tuberculoid [BT], Borderline [BB], and borderline lepromatous [BL]) which have intermediate clinical and immunological forms. The complete spectrum consists of TT, BT, BB, BL, and LL. Histopathological examination of skin lesions is often useful in confirming the classification.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Chemoprophylaxis with single-dose rifampicin New option for which we found one RCT comparing chemoprophylaxis with single-dose rifampicin versus placebo in contacts of people with leprosy. [13] It found that rifampicin reduced the number of contacts with a diagnosis of leprosy at 1 to 2 years compared with placebo, but it found no significant difference between the groups in new cases of leprosy at 3 to 4 years. Categorised as Beneficial.

Bacillus Calmette–Guerin One systematic review (search date 2006) added, which compared Bacillus Calmette–Guerin (BCG) versus placebo or no treatment , [17] and one RCT added, which compared BCG revaccination versus no BCG revaccination. [20] The systematic review of experimental and observational studies found that BCG vaccine reduced the proportion of people with leprosy compared with no BCG vaccine. [17] The RCT found no significant difference between BCG revaccination and no BCG revaccination, which contradicts previous RCT evidence. Categorisation unchanged (Beneficial). [20]

Multidrug treatment for multibacillary leprosy One case series added, [30] which found that relapse rates were 8% after at least 2 years of multidrug treatment (MDT) at an average of 1 to 17 years' follow-up. One RCT also added to the comments section, [33] which compared four regimens: 1 year of MDT, 1 year of MDT plus 1 month of rifampicin and ofloxacin; 1 month of rifampicin and ofloxacin; and 2 years of MDT. The RCT found no significant difference between the 1-year MDT groups and the 2-year MDT group, which supports the 1998 7th Expert Committee option of reducing the length of MDT from 24 months to 12 months. Categorisation unchanged (Likely to be beneficial by consensus).

Multidrug treatment for paucibacillary leprosy One retrospective case series added to the harms section, [40] which found that adverse effects occurred in 45% of people, and that 24% of people stopped taking dapsone. Categorisation unchanged (Likely to be beneficial by consensus).

***Mycobacterium w* vaccine** Reassessment of the reported evidence led to a change in categorisation from Unlikely to be beneficial to Likely to be beneficial. Evidence suggests that *Mycobacterium w* vaccine is more effective than placebo at reducing the incidence of leprosy, and we don't know how *Mycobacterium w* vaccine compares with ICRC or BCG (alone or with killed *M leprae*) vaccines as we have not identified direct comparisons between vaccines.

REFERENCES

1. WHO Expert Committee on Leprosy. *World Health Organ Tech Rep Ser* 1988;768:1–51.[PubMed]
2. Global leprosy situation, 2009. *Wkly Epidemiol Rec* 2009;84:333–340.[PubMed]
3. WHO Expert committee on Leprosy. Seventh Report. WHO Technical Report Series, No 874, 1998.
4. Fine PE. Leprosy: the epidemiology of a slow bacterium. *Epidemiol Rev* 1982;4:161–188.[PubMed]
5. Desikan KV, Sreevatsa. Extended studies on the viability of *Mycobacterium leprae* outside the human body. *Lepr Rev* 1995;66:287–295.
6. Lienhardt C, Kamate B, Jamet P, et al. Effect of HIV infection on leprosy: a three-year survey in Bamako, Mali. *Int J Lepr Other Mycobact Dis* 1996;64:383–391.[PubMed]
7. Lawn SD, Lockwood DNJ. Leprosy after starting antiretroviral treatment. *BMJ* 2007;334;217–218.[PubMed]
8. Ustianowski AP, Lawn SD, Lockwood DNJ. Interactions between HIV infection and leprosy: a paradox. *Lancet Infect Dis* 2006;6:350–360.[PubMed]
9. Croft RP, Richardus JH, Nicholls PG, et al. Nerve function impairment in leprosy: design, methodology, and intake status of a prospective cohort study of 2664 new leprosy cases in Bangladesh (The Bangladesh Acute Nerve Damage Study). *Lepr Rev* 1999;70:140–159.[PubMed]
10. Saunderson P, Gebre S, Desta K, et al. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev* 2000;71:285–308.[PubMed]
11. Pfaltzgraff R, Ramu G. Clinical leprosy. In: Hastings R ed. *Leprosy*. Edinburgh: Churchill Livingstone, 1994:237–287.
12. van Brakel WH. Peripheral neuropathy in leprosy and its consequences. *Lepr Rev* 2000;71:S146–S153.[PubMed]
13. Moet FJ, Pahan D, Oskam L, et al. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ* 2008;336:761–764.[PubMed]
14. Bakker MI, Hatta M, Kwenang A, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *Am J Trop Med Hyg* 2005;72:443–448.[PubMed]
15. Oo KN, Yin NN, Han TT, et al. Serological response to chemoprophylaxis in extended contacts in leprosy: a randomized controlled trial. *Nihon Hansenbyo Gakkai Zasshi: Japan J Leprosy* 2008;77:3–10.[PubMed]
16. Setia MS, Steinmaus C, Ho CS, et al. The role of BCG prevention of leprosy: a meta-analysis. *Lancet Infect Dis* 2006;6:162–170.[PubMed]
17. Zodpey SP. Protective effect of bacillus Calmette Guerin (BCG) vaccine in the prevention of leprosy: a meta-analysis. *Indian J Dermatol Venereol Leprol* 2007;73:86–93.[PubMed]
18. Lwin K, Sundaresan T, Gyi MM, et al. BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma. *Bull World Health Organ* 1985;63:1069–1078.[PubMed]
19. Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* 1996;348:17–24.[PubMed]
20. Cunha SS, Alexander N, Barreto ML, et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. *PLoS Negl Trop Dis* 2008;2:e167.[PubMed]
21. Bagshawe A, Scott GC, Russell DA, et al. BCG vaccination in leprosy: final results of the trial in Karimui, Papua New Guinea, 1963–79. *Bull World Health Organ* 1989;67:389–399.[PubMed]
22. Gupte MD, Vallishayee RS, Anantharaman DS, et al. Comparative leprosy vaccine trial in south India. *Indian J Lepr* 1998;70:369–388.[PubMed]
23. Sharma P, Mukherjee R, Talwar GP, et al. Immunoprophylactic effects of the anti-leprosy *Mw* vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8–10 years. *Lepr Rev* 2005;76:127–143.[PubMed]
24. Dasananjali K, Schreuder PA, Pirayavaraporn C. A study on the effectiveness and safety of the WHO/MDT regimen in the northeast of Thailand; a prospective study, 1984–1996. *Int J Lepr Other Mycobact Dis* 1997;65:28–36.[PubMed]
25. Gebre S, Saunderson P, Byass P. Relapses after fixed duration multiple drug therapy: the AMFES cohort. *Lepr Rev* 2000;71:325–331.[PubMed]
26. Schreuder PA. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1987–1995 [correction of 1978–1995]. I. Overview of the study. *Int J Lepr Other Mycobact Dis* 1998;66:149–158.[PubMed]
27. Li HY, Hu LF, Hauang WB, et al. Risk of relapse in leprosy after fixed duration multi-drug therapy. *Int J Lepr Other Mycobact Dis* 1997;65:238–245.[PubMed]
28. Girdhar BK, Girdhar A, Kumar A. Relapses in multibacillary leprosy patients: effect of length of therapy. *Lepr Rev* 2000;71:144–153.[PubMed]
29. Shaw IN, Natrajan MM, Rao GS, et al. Long-term follow up of multibacillary leprosy patients with high BI treated with WHO/MDT regimen for a fixed duration of two years. *Int J Lepr Other Mycobact Dis* 2000;68:405–409.[PubMed]
30. Medeiros S, Catorze MG, Vieira MR. Hansen's disease in Portugal: multibacillary patients treated between 1988 and 2003. *J Eur Acad Dermatol Venereol* 2009;23:29–35.[PubMed]
31. World Health Organization. A guide to leprosy control. 2nd Ed: WHO. Geneva: WHO, 1988.
32. Yawalkar SJ, McDougall AC, Languillon J, et al. Once-monthly rifampicin plus daily dapsone in initial treatment of lepromatous leprosy. *Lancet* 1982;1:1199–1202.[PubMed]
33. Fajardo TT, Villahermosa L, Pardillo FE, et al. A comparative clinical trial in multibacillary leprosy with long-term relapse rates of four different multidrug regimens. *Am J Trop Med Hyg* 2009;81:330–334.[PubMed]
34. Lockwood DN. The management of erythema nodosum leprosum: current and future options. *Leprosy Rev* 2006;67:253–259.[PubMed]
35. WHO. Chemotherapy of leprosy. Report of a WHO study group. WHO Technical Report Series, No 847, 1994.
36. Kar PK, Arora PN, Ramasastry CV, et al. A clinicopathological study of multidrug therapy in borderline tuberculoid leprosy. *J Indian Med Assoc* 1994;92:336–337.[PubMed]

37. Boerrigter G, Ponnighaus JM, Fine PE. Preliminary appraisal of a WHO-recommended multiple drug regimen in paucibacillary leprosy patients in Malawi. *Int J Lepr Other Mycobact Dis* 1988;56:408–417.[PubMed]
38. Chopra NK, Agarawal JS, Pandya PG. A study of relapse in paucibacillary leprosy in a multidrug therapy project, Baroda District, India. *Lepr Rev* 1990;61:157–162.[PubMed]
39. Boerrigter G, Ponnighaus JM, Fine PE, et al. Four-year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *Int J Lepr Other Mycobact Dis* 1991;59:255–261.[PubMed]
40. Deps PD, Nasser S, Guerra P, et al. Adverse effects from multi-drug therapy in leprosy: a Brazilian study. *Leprosy Rev* 2007;78:216–222.[PubMed]
41. Ji B. Drug resistance in leprosy – a review. *Lepr Rev* 1985;56:265–278.[PubMed]
42. Single-lesion Multicentre Trial Group. Efficacy of single-dose multidrug therapy for the treatment of single-lesion paucibacillary leprosy. *Indian J Leprosy* 1997;69:121–129.
43. Pattyn SR. A randomized clinical trial of two single-dose treatments for paucibacillary leprosy. *Lepr Rev* 1994;65:45–57.[PubMed]

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Competing interests: PS is the co-author of one RCT and two case series reports referenced in this review. WCS is co-author of a cohort study, was a member of the WHO Expert Committee, and a member of the research group.

Disclaimer

TABLE 1 **Case series of dapsone plus rifampicin plus clofazimine in multibacillary leprosy and paucibacillary leprosy: clinical outcomes and relapse rates.**

Ref	Location	Participants	Follow-up (years)	Clinical outcome		
				Skin lesions	Nerve impairment	Relapse rates
Multibacillary leprosy						
[24]	Thailand	53 people with multibacillary leprosy	8 (range 2–8)	Clinically active at about 3 years: 14/49 (29%)	Grade 2 disability: Start of treatment: 8% End of treatment: 13%	0/53 (0%) 0/1000 PYAR
[25]	Ethiopia	256 with multibacillary leprosy (57 people with BI greater than 4 at enrolment)	4.3 (range 0–8.6); 38% followed up for at least 5 years	No data	No data	0/256 (0%) 0/1000 PYAR
[26]	Thailand	220 people with multibacillary leprosy	3	No data	No data	2/198 (1%) 3.3/1000 PYAR
[27]	China	5981 people with multibacillary leprosy	Range 1 to 10	No data	No data	5/5981 (0.1%) 0.19/1000 PYAR
[28]	India	287 people with multibacillary leprosy	Range 1 to 8	No data	No data	20/260 (8%) 20.4/1000 PYAR 18/20 (90%) with BI greater than 4 at enrolment
[29]	India	65 people with multibacillary leprosy	Greater than 5; 76% followed up for at least 7 years	No data	No data	1/46 (2%) 0.023/1000 PYAR
[30]	Portugal	112 people with multibacillary leprosy	Range 1 to 17 (mean 5.5)	No data	96% of people had neurological pathology (nerve enlargement, "papal hand" and "claw hand" flexion, sensory-motor neuropathy, and foot drop). Relapse was not associated with peripheral neuropathy or disability	9/112 (8%)
Paucibacillary leprosy						
[24]	Thailand	123 people with paucibacillary leprosy	8.2 (range 1–10)	Clinically active at about 3 years: 27/123 (22%)	Grade 2 disability: Start of treatment: 4% End of treatment: 7%	2/112 (2%) 2/1000 PYAR
[25]	Ethiopia	246 people with multibacillary leprosy	4.1 (range 0–8.8); 39% followed up for at least 5 years	No data	No data	0/246 (0%) 0/1000 PYAR
[26]	Thailand	420 people with paucibacillary leprosy	5	No data	No data	8/393 (2%) 4.1/1000 PYAR
[27]	China	2326 people with paucibacillary leprosy	Range 1 to 5	No data	No data	5/2326 (0.2%) 0.55/1000 PYAR A further 6 people self-reported relapse after the 5-year surveillance period

Ref	Location	Participants	Follow-up (years)	Clinical outcome		
				Skin lesions	Nerve impairment	Relapse rates
[36]	India	50 people with paucibacillary leprosy	0.5	Clinically inactive: 4/50 (8%) Marked clinical improvement (reduction in size of lesion of greater than 1 cm, disappearance of erythema and/or infiltration or disappearance of satellite lesions): 16/50 (32%) Clinical regression (reduction in size of lesion of less than 1 cm, decrease in erythema and/or infiltration of the lesion): 22/50 (44%) Increase in clinical activity (appearance of new lesions, increased erythema or infiltration, and/or development of thickening and/or tenderness of the peripheral nerve):	No data	No data
[37] [39]	Malawi	499 people with paucibacillary leprosy	4	At 1 year: Lesions no longer evident: 180/473 (38%) Lesions visible but not active: 282/473 (60%) Lesions visible and active: 11/473 (2%)	New disability: 12/482 (2%) Worsening of disability: 16/482 (3%)	12/499 (2%) 6.5/1000 PYAR
[38]	India	10,095 people with paucibacillary leprosy	5	No data	Of people with relapse: 1/21 (5%) had grade 1 deformity 2/21 (10%) had grade 2 deformity 1/21 (5%) had grade 3 deformity	21/10,995 (0.2%)

BI, bacterial index, PYAR, person-years at risk; Ref, reference.

TABLE **GRADE evaluation of interventions for leprosy**

Important outcomes		Incidence of leprosy, clinical improvement, relapse rate, quality of life, adverse effects							
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent leprosy?									
1 (21,711) [13]	Incidence of leprosy	Single-dose rifampicin *v* placebo	4	0	–1	0	0	Moderate	Consistency point deducted for different results at different time points
At least 29 (at least 625,185) [16] [17] [18]	Incidence of leprosy	BCG vaccine *v* placebo or no treatment	4	–1	–1	0	0	Low	Quality point deducted for inclusion of observational data. Consistency point deducted for heterogeneity among studies
2 (213,790) [19] [20]	Incidence of leprosy	BCG revaccination *v* no BCG revaccination	4	–1	–1	–1	0	Very low	Quality point deducted for methodological issues. Consistency point deducted for conflicting results. Directness point deducted for multiple interventions in comparison
1 (76,926) [22]	Incidence of leprosy	BCG vaccine plus killed *M leprae* *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (121,020) [19]	Incidence of leprosy	BCG vaccine plus killed *M leprae* *v* BCG alone	4	0	0	0	0	High	
1 (22,541) [22]	Incidence of leprosy	ICRC vaccine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (63,140) [23] [22]	Incidence of leprosy	*Mycobacterium w* vaccine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatments for leprosy?									
2 (165) [24] [30]	Clinical improvement	Multidrug treatment for multibacillary leprosy	2	–1	0	0	0	Very low	Quality point deducted for sparse data
7 (6974) [24] [25] [26] [27] [28] [29] [30]	Relapse rate	Multidrug treatment for multibacillary leprosy	2	0	0	0	0	Low	
4 (10,767) [24] [36] [37] [39] [38]	Clinical improvement	Multidrug treatment for paucibacillary leprosy	2	0	–1	0	0	Very low	Consistency point deducted for use of different methods of assessment
6 (13,759) [24] [25] [26] [27] [39] [38]	Relapse rate	Multidrug treatment for paucibacillary leprosy	2	0	–1	0	0	Very low	Consistency point deducted for use of different methods of assessment
1 (1483) [42]	Clinical improvement	Single-dose antibiotics *v* multiple-dose antibiotics	4	–2	0	0	0	Low	Quality points deducted for diagnostic uncertainty and short follow-up

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.